SYNOPSIS OF RESEARCH REPORT [redacted]
(PROTOCOL BA16736 - FINAL)

COMPANY: F.Hoffman-La Roche Ltd NAME OF FINISHED PRODUCT: RO0503821 NAME OF ACTIVE SUBSTANCE(S): RO0503821	(FOR NATIONAL AUTHORITY USE ONLY)

TITLE OF THE STUDY / REPORT No. / DATE OF REPORT	Protocol BA16736: An open-label, randomized, multi-center, parallel group study to demonstrate correction of anemia using intravenous injections of RO0503821 in patients with chronic kidney disease (CKD) who are on dialysis. Report [redacted] December 2006		
INVESTIGATORS / CENTERS AND COUNTRIES	This study was conducted by 42 investigators/sites in 10 countries: Poland, Russia, South Africa, Brazil, Canada, Thailand, Greece, Czech Republic, Spain and USA		
PUBLICATION (REFERENCE)	None		
PERIOD OF TRIAL	First Patient Screened: 29 March 2004 Last Patient Last Observation: December 8, 2005	CLINICAL PHASE	III
OBJECTIVES	Primary objective: • To demonstrate the efficacy of intravenous (IV) RO0503821 treatment for correction of anemia in patients with CKD who are on dialysis Secondary objectives: • To assess time to response • To assess the safety and tolerability of multiple doses of RO0503821 during the correction and extension periods in this patient population • To assess long-term safety with RO0503821 in this patient population • To investigate the pharmacokinetics and the concentration-effect relationships after IV administration of RO0503821 in this patient population		
STUDY DESIGN	Open-label, randomized, multi-center study with one dosing interval (1×/2 weeks) during the correction period and two dosing intervals (1×/2 weeks, 1×/4 weeks) during the extension period; non-comparative reference group. The primary and secondary efficacy endpoints were assessed at the end of the correction period; the purpose of the extension period was to document long-term safety.		

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NUMBER OF SUBJECTS	Entered Correction Period: 181 patients 135 RO0503821 46 Epoetin Entered Extension Period: 163 patients 61 RO0503821 1x/2 weeks 62 RO0503821 1x/4 weeks 40 Epoetin	Completed Correction Period: 164 patients 124 RO0503821 40 Epoetin Completed Extension Period: 142 patients 53 RO0503821 1x/2 weeks 54 RO0503821 1x/4 weeks 35 Epoetin
DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION	Adult patients with chronic renal anemia who were on dialysis and not currently receiving treatment with an erythropoiesis-stimulating agent.	
TRIAL DRUG / STROKE (BATCH) No.	RO0503821: [redacted]	
DOSE / ROUTE / REGIMEN / DURATION	Correction Period: IV injections of 0.4 µg/kg of RO0503821 once every two weeks (1×/2 weeks). The target hemoglobin (Hb) concentration during the correction period (weeks 1-24) was ≥ 11.0 g/dL and an increase in Hb from baseline of ≥ 1.0 g/dL. In case of inadequate response to RO0503821, dose adjustments could be performed every 4 weeks. Extension Period: Patients who achieved the target Hb concentration in the correction period were re-randomized to either RO0503821 1×/2 weeks or RO0503821 1×/4 weeks. The dose of RO0503821 was adjusted to maintain the individual patient's Hb within a target range of 11.0 to 13.0 g/dL.	
REFERENCE DRUG / STROKE (BATCH) No.	Epoetin alfa (human albumin-containing formulation) or epoetin beta in single or multi- dose vials	
DOSE / ROUTE / REGIMEN / DURATION	Correction Period: Three IV injections of epoetin alfa or beta administered according to approved labeling. The target Hb concentration during the correction period (weeks 1-24) was ≥ 11.0 g/dL and an increase in Hb from baseline of ≥ 1.0 g/dL. In case of inadequate response to epoetin, dose adjustments could be performed. Extension Period: During the extension period, patients in the epoetin group remained on the same treatment regimen. The dose of epoetin was adjusted	

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	to maintain the individual patient's Hb within a target range of 11.0 to 13.0 g/dL.
CRITERIA FOR EVALUATION	
EFFICACY:	The primary efficacy endpoint was the Hb response rate. The assessment of response was based on the weekly Hb measurements and defined as an increase in Hb ≥ 1.0 g/dL from baseline and a single Hb concentration ≥ 11 g/dL, without red blood cell (RBC) transfusion before response, during the 24 weeks after first dose (until day 173).
EFFICACY (Cont.):	The secondary efficacy endpoints were: • The Hb values and their changes from baseline over time • The time to Hb response assessed via Kaplan-Meier methods • The incidence of RBC transfusions during the first 24 weeks
PHARMACODYNAMICS:	Not applicable
PHARMACOKINETICS:	Serum concentrations of RO0503821, RBC count, absolute reticulocyte count, and hemoglobin were used to evaluate the pharmacokinetics and the concentration-effect relationships in a subset of patients
SAFETY:	Safety parameters included adverse events (AEs), safety hematology and blood chemistry (including iron) laboratory tests, assessment of dialysis adequacy, anti-erythropoietin antibody testing, vital signs and 12-lead ECGs.
STATISTICAL METHODS	The primary efficacy endpoint was the Hb response rate (r). The assessment of response was based on the weekly Hb measurements and defined as an increase in Hb ≥ 1.0 g/dL from baseline and a Hb concentration ≥ 11.0 g/dL without RBC transfusion during the 24 weeks after the first dose. The average baseline value was estimated by calculating the mean of all values recorded between the day of first dose and the previous 20 days. The value on the day of the first dose was included in the baseline calculation, as this assessment was performed before the first dose is given. The study was to demonstrate that the response rate was at least 60% in the RO0503821 group. A two-sided 95% confidence interval based on the exact method of Clopper and Pearson was calculated. If the lower limit of this confidence interval was above 60%, H_0 (H_0: $r \leq 60\%$) could be rejected with a significance level of 0.025 (one sided). This would allow the conclusion that RO0503821 administered 1×/2 weeks results in correction of anemia. The secondary efficacy endpoints were:

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- The Hb values and their changes from baseline over time
- The time to Hb response assessed via Kaplan-Meier methods
- The incidence of RBC transfusions during the first 24 weeks

Hemoglobin values and change from baseline over time and the incidence of RBC transfusions were summarized using descriptive methods. Hb values over time were also summarized descriptively during the extension period.

Safety data were summarized descriptively.

METHODOLOGY:

After written informed consent was obtained, patients were screened for eligibility during a 2-week period (weeks -2 to -1). Eligible patients were randomized in a 3:1 ratio to receive either RO0503821 0.4 µg/kg IV every 2 weeks or to epoetin 3×/week IV. The study consisted of a correction period (dose titration) of 24 weeks, followed by an extension period of up to 28 weeks for documentation of safety. At week 25, after 24 weeks of treatment, the responders in the RO0503821 group (defined as patients who reach the target Hb) were re-randomized either to RO0503821 1×/2 weeks or RO0503821 1×/4 weeks. Patients were kept on this treatment regimen for the subsequent 28 weeks. Patients in the reference group were kept on their original dosing regimen for the subsequent 28 weeks.

EFFICACY RESULTS:

Primary Endpoint:

- For the intention-to-treat population, 126 patients (93%) RO0503821 were responders, and the lower limit of the 95% CI for the response rate was higher than 60% (95% CI 87.7-96.9, $p<0.0001$). The high overall response rate allows the conclusion that RO0503821 administered IV 1×/2 weeks results in correction of anemia. Results were consistent for the per-protocol population and eligible populations.

Secondary Endpoints:

- Median Hb concentrations increased in both the RO0503821 group and the epoetin group, although the increase was more rapid in the epoetin group compared with the RO0503821 group.
- The median time to Hb response was 57 days in the RO0503821 group and 31 days in the epoetin group.
- Seven patients (5.2%) in the RO0503821 group and two patients (4.3%) in the epoetin group received RBC transfusions during the correction period.

Extension Period:

Median Hb concentrations were generally lower in the RO0503821 1x/4 weeks group (range 11.0-12.1 g/dL) compared with the RO0503821 1x/2 weeks and epoetin groups (range 11.9-12.5 g/dL and 11.6-12.3 g/dL, respectively). Despite the lower Hb concentrations in the RO0503821 1x/4 weeks group, the incidence of RBC transfusions was not higher compared with the RO0503821 1x/2 weeks and epoetin groups. Moreover, no patients were withdrawn due to lack of efficacy during the extension period. Although the median numbers of dose changes during the extension period were similar, more patients in the RO0503821 1x/4 weeks group had dose increases and the median weekly equivalent dose of

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RO0503821 was higher in the 1x/4 weeks group (mostly around 0.30 µg/kg/week) compared with the 1x/2 weeks group (0.20-0.24 µg/kg/week).

PHARMACOKINETIC RESULTS:

Pharmacokinetic analyses are provided in a separate report.

SAFETY RESULTS:

Correction Period:

The overall incidence of AEs was similar between the two treatment groups: 72% of patients in the RO0503821 group and 78% of patients in the epoetin group experienced at least one AE. Adverse events for patients in the RO0503821 and epoetin groups, respectively, occurred most frequently in the following SOCs: injury, poisoning and procedural complications (27% and 39%), vascular disorders (27% and 35%), infections and infestations (26% and 33%) and gastrointestinal disorders (27% and 13%). Hypertension was the most common AE (19% and 24% in the RO0503821 and epoetin groups, respectively), followed by procedural hypotension (7% of patients in both groups) and arteriovenous fistula thrombosis (5% and 9% of patients in the RO0503821 and epoetin groups, respectively). The majority of AEs reported were of mild or moderate intensity and assessed as unrelated to study medication.

Serious AEs were reported for a higher proportion of patients in the RO0503821 group than in the epoetin group (22% vs. 15%). The incidence of severe/life-threatening AEs was higher in the RO0503821 group compared with the epoetin group (17.8% vs. 8.7%). Although there were more SAEs and severe/ life-threatening AEs reported in the RO0503821 group compared with the epoetin group, this imbalance was not due to any specific event, but multiple events reported in single patients. SAEs for patients in the RO0503821 and epoetin groups, respectively, occurred most frequently in the following SOCs: injury, poisoning and procedural complications (4% of patients in both groups), vascular disorders (4% and 2%) and infections and infestations (4% and 2%). Two patients had SAEs that were considered to be related to the study medication (one patient in each treatment group).

One patient withdrew from the study due to an AE (chronic renal failure - withdrawal of dialysis); this event was not considered to be related to the study medication.

Two patients, both in the RO0503821 group, died during the correction period. Causes of death were aspiration pneumonia and chronic renal failure (withdrawal of dialysis treatment). Neither of these events was considered by the investigator to be related to the study medication.

Extension Period:

During the extension period, the incidence of AEs was 62% in the RO0503821 1x/2 weeks group, 81% in the RO0503821 1x/4 weeks group and 75% in the epoetin group. Although the proportion of AEs was highest in RO0503821 1x/4 weeks group, the incidence of SAEs was not higher. SAEs were reported for 26%, 16% and 28% of patients in the RO0503821 1x/2 weeks, RO0503821 1x/4 weeks and epoetin groups, respectively. Infections and infestations were the most commonly reported AEs (by 25%, 35% vs 35%). The most commonly reported individual AEs were muscle spasms and hypertension. Muscle spasms were reported for 7%, 11% vs 5% of patients and hypertension was reported for 5%, 10% vs 8% of patients. Related AEs were reported for 3%, 2% vs 8%. Of these, two patients in the RO0503821 1x/2 weeks group had SAEs that were considered to be related to the study medication (arteriovenous graft thrombosis and transient ischemic attack).

Nine patients died during the extension period: two patients (3%) in the RO0503821 1x/2 weeks group,

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three patients (5%) in the RO0503821 1x/4 weeks group and four patients (10%) in the epoetin group. None of the deaths were considered to be related to the study medication. Two deaths (pneumonia and thrombotic stroke), both in the RO0503821 1x/4 weeks group, were associated with a change in Hb of > 2.0 g/dL in the 4 weeks preceding the event. No other events were associated with Hb concentrations < 10.0 g/dL or > 13.5 g/dL within the 2 weeks preceding the event or a change of > 2.0 g/dL in the 4 weeks before the event.

Complete study period

During the complete study period, the incidence of AEs was similar between the pooled RO0503821 group and the epoetin group (87% vs. 85%, respectively) and the types of AEs recorded were characteristic of the patient population. Adverse events were reported most frequently in the following SOCs: infections and infestations (42% RO0503821 vs 52% epoetin), injury, poisoning and procedural complications (37% RO0503821 and 48% epoetin) and vascular disorders (35% RO0503821 vs 41% epoetin). Hypertension was the single most common AE and was reported for 21% of patients in the RO0503821 group and 28% in the epoetin group. Similar proportions of patients in both groups had SAEs (34% and 35% in the RO0503821 and epoetin groups, respectively). A total of 16% of patients in the RO0503821 group and 20% of patients in the epoetin group had AEs that were considered to be related to the study medication. Of these, three patients had related SAEs: two patients (2%) in the RO0503821 group (arteriovenous graft thrombosis and transient ischemic attack) and one patient (2%) in the epoetin group (arteriovenous fistula thrombosis).

Eleven patients died during the study: seven patients (5%) in the RO0503821 group and four patients (9%) in the epoetin group. None of the deaths were considered to be related to the study medication. Three deaths (pneumonia and thrombotic stroke in the RO0503821 group and aortic dissection in the epoetin group) were associated with a change in Hb of > 2.0 g/dL in the 4 weeks preceding the event. No other events were associated with Hb concentrations < 10.0 g/dL or > 13.5 g/dL within the 2 weeks preceding the event or a change of > 2.0 g/dL in the 4 weeks before the event.

Throughout the study period, there were no apparent differences or trends of significance in any of the laboratory parameters except in the platelets, which were slightly lower in the RO0503821 compared with the epoetin arm. There were no apparent differences between the treatment groups with respect to vital signs or ECG changes. No anti-erythropoietin or anti-RO0503821 antibodies were detected in any patients.

CONCLUSIONS:

Intravenous RO0503821 was effective in correcting anemia in patients with chronic kidney disease who were on dialysis. Dose adjustments of RO0503821, according to protocol guidance, enabled correction of anemia to target Hb levels, but a starting dose similar to that at which correction was achieved (median dose of 0.6 µg/kg/q2w) might be preferable. During the extension period, median Hb levels were slightly lower in the RO0503821 1x/4 weeks group compared with the RO0503821 1x/2 weeks and epoetin groups.

Long-term administration of IV RO0503821 in patients with CKD who are on dialysis was generally well-tolerated. The safety profile of RO0503821 was similar when given once every 2 weeks or once every 4 weeks. Safety findings were characteristic of the study population and were generally comparable between treatment groups.